tion of the *trans*-acid began soon after the heating started. On cooling, 0.75 g. of product separated and was filtered off.

n-Butyl N-carbamylmaleamate (IV. R = H, R′ = *n*-C_4H_9). A mixture of 1184 g. of *n*-butanol, 560 g. (4.0 mol.) of IIIa, 8 g. of zinc chloride and 150 g. of petroleum ether (b.p. 60–70°) was refluxed at 85° until solution was complete. The solution was filtered and cooled, depositing 782 g. (92%) of the ester, m.p. 96–99°.

Methyl N-carbamylfumaramate. Addition of 0.1 g. of aluminum chloride to 5.0 g. (0.036 mol.) of IIIa in 50 ml. of methanol caused an immediate exothermic reaction and precipitation of a quantitative yield of methyl *N*-carbamylfumaramate, m.p. 228–230°.

Copolymerization of IIIa *with vinyl acetate.* A solution of 10 g. (0.07 mol.) of IIIa, 25 ml. (0.27 mol.) of vinyl acetate and 0.1 g. of benzoyl peroxide in 194 ml. of dioxane was heated at 80° in a water bath for 6 hr. The polymer solution was poured into 1 l. of acetone. After filtration and drying, the polymer weighed 5.5 g. (17% conversion), was soluble in dimethylformamide and, with hydrolysis, in 10% aqueous sodium hydroxide, had intrinsic viscosity 0.13 and analyzed for 57.6% nitrogen. This analysis corresponds to a ratio of IIIa to vinyl acetate of 1:1.2 from a feed ratio of 1:3.8.

Copolymerization of methyl N-carbamylmaleamate (IV. R = H, R′ = CH_3) *with styrene.* A mixture of 20 g. (0.192 mol.) of styrene, 20 g. (0.116 mol.) of IV and 0.8 g. of benzoyl peroxide in 40 g. of acetone was heated for 4.75 hr. in a water bath held at 70°. The clear solution, which still contained some undissolved IV, was poured into stirred methanol to precipitate the polymer. The precipitate was filtered off and dried overnight in an evacuated desiccator. The material was then triturated with methanol and again dried overnight in a vacuum desiccator. The product weighed 11.6 g. (29% conversion) and was soluble in dioxane and acetic acid. Nitrogen analysis (6.05, 6.05%) indicated that the monomer ratio (IV:styrene) in the polymer was 1:2.8 from a feed ratio of 1:1.65. The polymer had an intrinsic viscosity in dioxane of 0.11.

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WAYNE, N. J.

[CONTRIBUTION FROM THE RESEARCH INSTITUTE OF TEMPLE UNIVERSITY AND THE RESEARCH AND DEVELOPMENT DIVISION SMITH KLINE & FRENCH LABORATORIES]

Synthesis of Phenothiazines. III. Derivatives of Hydroxy- and Mercaptophenothiazines[1]

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The preparation of seven phenothiazines is reported; they are 2-hydroxy-, 2-benzoyloxy-, 2-methylmercapto-, 2- and 4-trifluoromethylmercapto-, 2-methylsulfonyl-, and 2-trifluoromethylsulfonylphenothiazine. Various new intermediates are described.

The early French work in the phenothiazine field, following the lead of chloropromazine, resulted in the synthesis of the 2-methyl and 2-methoxy derivatives.[4] Further work in France[5] and in Switzerland,[6] as well as independent work in our laboratories, produced the 2-methylmercapto- and 2-methylsulfonyl-phenothiazines. The development of the potent 10-aminoalkyl-2-trifluoromethylphenothiazines[7,8] has led us to study the 10-aminoalkyl-2-trifluoromethylmercapto- and 2-trifluoromethylsulfonylphenothiazines. The present paper describes the preparation of the novel 2-substituted phenothiazine intermediates. The synthesis of a number of 10-alkylated phenothiazines derived from them will be described later.

Many methods for preparing phenothiazines have been reported in the literature.[9] These include: (A) the thionation of an appropriately substituted diphenylamine with sulfur[10] and a catalyst,[11,12] (B) the copper-catalyzed dehydrohalogenation of substituted 2-amino-2′-halodiphenyl sulfides,[13] and (C) the Smiles rearrangement of 2′-amido-2-

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(1) These compounds were prepared at the Research Institute of Temple University under a contract with Smith Kline & French Laboratories. Papers I and II of this series are considered to be those referred to in ref. (7) and (34).

(a) To whom inquiries may be addressed.

(2) Research Institute of Temple University.

(3) Smith Kline & French Laboratories.

(4) P. Charpentier, *et al.*, *Compt. rend.*, **235**, 59 (1952).

(5) Rhône-Poulenc, Belgian Patent **552,836** (1957).

(6) J.-P. Bourquin, G. Schwarb, G. Gamboni, R. Fisher, L. Ruesch, S. Guldimann, V. Theus, E. Schenker, and J. Renz, *Helv. Chim. Acta*, **41**, 1061 (1958).

(7) P. N. Craig, E. A. Nodiff, J. J. Lafferty, and G. E. Ullyot, *J. Org. Chem.*, **22**, 709 (1957).

(8) H. L. Yale, F. Sowinski, and J. Bernstein, *J. Am. Chem. Soc.*, **79**, 4375 (1957).

(9) S. P. Massie, *Chem. Revs.*, **54**, 797 (1954).

(10) A. Bernthsen, *Ber.*, **16**, 2896 (1883).

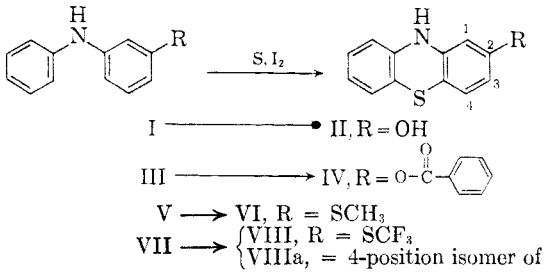
(11) E. Knoevenagel, *J. prakt. Chem.*, **89**, 11 (1914).

(12) F. Ackermann, German Patent **224,348** (1909).

(13) P. J. C. Buisson, P. Gailliot, and J. Gaudechon, U. S. Patent **2,769,002** (1956).

nitrodiphenyl sulfides followed by ring closure with loss of nitrous acid.[14,15]

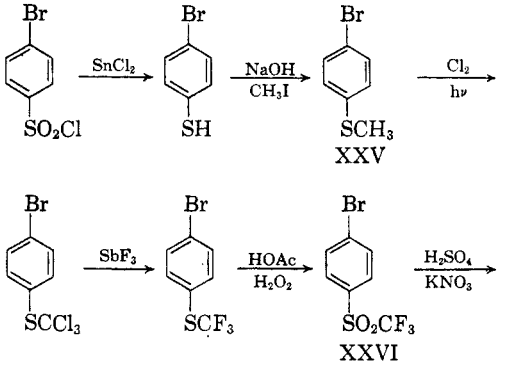
Five of the phenothiazines reported here were made by method (A) using the appropriate 3-substituted diphenylamines as shown by the accompanying equation. Single attempts to prepare 2-methylsulfonyl- and 2-acetoxyphenothiazine, using Method (A), gave evolution of hydrogen sulfide, but no phenothiazines could be characterized in the products of the reactions.

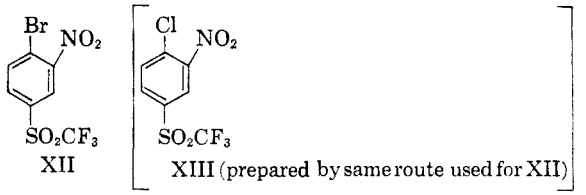


The reaction of resorcinol with aniline in the presence of calcium chloride gave the 3-hydroxydiphenylamine (I).[16,17] The benzoate (III)[18] and the acetate (X) were prepared from I. The remaining diphenylamines were prepared by the method of Goldberg[19] from acetanilide and the appropriately 3-substituted bromobenzenes.

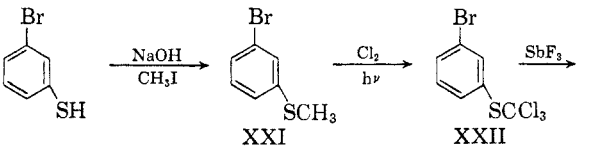
Two other phenothiazines were prepared according to Method (B), starting with *o*-bromothiophenol and the appropriately substituted *o*-halonitrobenzenes.

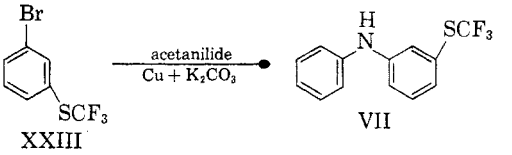
The routes used to prepare some of the required intermediates are outlined in the flow diagrams.

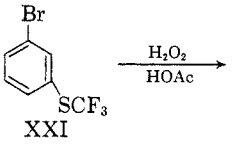


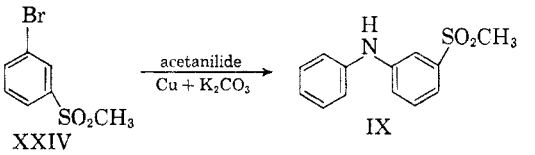


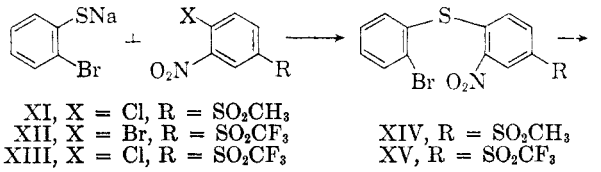
(14) W. J. Evans and S. Smiles, *J. Chem. Soc.*, 181 (1935).
(15) W. J. Evans and S. Smiles, *J. Chem. Soc.*, 1263 (1935).
(16) A. Calm, *Ber.*, **16**, 2786 (1883).
(17) V. Merz and W. Weith, *Ber.*, **14**, 2343 (1881).
(18) K. v. Auwers, *Ann.*, **364**, 171 (1909).
(19) I. Goldberg, *Ber.*, **40**, 4541 (1907).

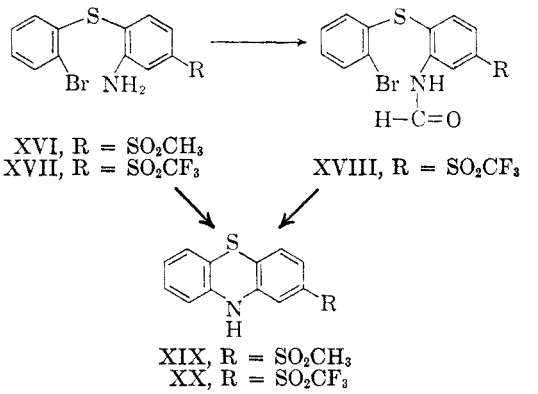












The preparation of most of the intermediates was routine. However, several points in these syntheses are of interest.

It was found that 2′-bromo-2-nitro-4-methylsulfonyldiphenylsulfide (XIV) exists in two crystalline modifications. These forms show identical elemental analyses but melt at 132–133° (α) and 158–160° (β). On standing overnight, at room temperature, exposed to air, the low melting form (α) converts to the high melting form (β). The melting point of the (β) form is not depressed upon admixture with the high melting form prepared from the (α) modification. The infrared spectra show some differences, but the work of Jones and

Sandorfy[20] and Ebert and Gottlieb[21] on spectra and polymorphism indicates that this is not unusual. In one reaction the products (XIV) were found to consist of 35% as the (α) modification and 55% as the (β) form. In a similar reaction the only compound isolated was 78% as the (α) form. On reduction and cyclization both forms gave the same amine (XVI) and the same phenothiazine (XIX).

The synthesis of 2′-bromo-2-nitro-4 trifluoromethylsulfonyldiphenylsulfide (XV) was accomplished, in one case, by the reaction between sodium *o*-bromothiophenolate and 3-nitro-4-chlorophenyl trifluoromethylsulfone (XIII) and, in another, by the same reaction using the bromo analog of XIII. The bromo analog (XII) gave a 92% yield of XV after refluxing in ethanol for four hours. The chloro compound (XIII) gave only a 46% yield of XV after refluxing for as long as eighteen hours.

The cyclization of 2′-bromo-2-amino-4-trifluoromethylsulfonyldiphenylsulfide (XVII) to 2-trifluoromethylsulfonylphenothiazine (XX) was very sensitive to time and to the purity of the starting material (XVII). Thus, starting material which melted 110–113° gave yields of XX of 30% or less, while material melting only slightly higher (112–113°) increased the yield to 60%. If XVII were refluxed in *N*,*N*-dimethylformamide (DMF) for longer than 6.5 hr. or if it were impure, the copper catalyst was partly consumed and XVII was converted to a purple substance which was soluble only in water and DMF. To eliminate the critical nature of this cyclization it was found expedient to formylate XVII. On cyclization, the formyl derivative (XVIII) gave 60–80% of the phenothiazine (XX) after refluxing for only 1.25 hr. The formyl group was removed during the reaction.[22]

The configuration of the phenothiazines (XIX and XX) obtained by Method (B) is unequivocal, as only one isomer is possible. Method (A), however, when applied to 3-substituted diphenylamines, can give both the 2- and 4-substituted phenothiazines, depending on whether thionation takes place *o*- or *p*- to the substituent. Various authors[4,6,8,9,22–24] have investigated this situation and from their work have proposed criteria for the assignment of structure. Thus the 2-isomer is obtained in greater abundance, is less soluble, and melts higher.[25] In the infrared the 2-isomers should show a deep band in region 12.0–12.5μ (asymmetric trisubstituted benzene) while the 4-isomers show a deep band in the region 12.5–13.2μ (vicinal trisubstituted benzenes).

The 2-methylmercapto-, 2-trifluoromethylmercapto- and 4-trifluoromethylmercaptophenothiazines show the expected peaks (12.4μ, 12.3μ and 12.8μ respectively). However, the unambiguously prepared 2 - methylsulfonylphenothiazine (XIX) has a very weak peak at 12.5μ and an unexpected strong peak at 13.0μ. The similarly prepared 2-trifluoromethylsulfonylphenothiazine (XX) has a moderate peak at 12.4μ but again an unexpected strong peak at 13.0μ. The benzoyloxy phenothiazine has only a weak peak at 12.6μ in the region 12.0–13.2μ. The final assignment of orientation in phenothiazines should not be made solely on the basis of infrared spectra.[22]

The phenothiazines reported here gave a characteristic deep red color with concentrated nitric acid except for 2-hydroxyphenothiazine, which gave a green color in this test.

EXPERIMENTAL[26]

3-Acetoxydiphenylamine (X).[27] Acetylation of 3-hydroxydiphenylamine (I)[16,17] was carried out with acetic anhydride in pyridine. Recrystallization from ethanol gave 80% of white crystals, m.p. 86–87°.

Anal. Calcd. for $C_{14}H_{13}NO_2$: C, 73.99; H, 5.77. Found: C, 73.99; H, 6.04.

2-Hydroxyphenothiazine (II). A mixture of 1.6 g. (0.0087 mol.) of I, 0.51 g. (0.016 mol.) sulfur and a few crystals of iodine was heated in a test tube, under dry nitrogen, for 1 hr. at 130–140°. The hard, black reaction mass was extracted with benzene and the extracts were concentrated and treated with petroleum ether to give a flocculent yellow precipitate. Vacuum sublimation, followed by recrystallization from benzene, gave 0.2 g. (11%) of pale yellow glistening platelets. It was not possible to get a clear melting point even under nitrogen. Successive portions of II were plunged into a melting point bath whose temperature was gradually increased. At a bath temperature of 215° the solid melted momentarily to a clear yellow liquid before decomposing (lit.,[27(a)] 207–209°).

Anal. Calcd. for $C_{12}H_9NOS$: C, 56.95; H, 4.21. Found: C, 57.07; H, 4.57.

3-Benzoyloxydiphenylamine (III). Benzoylation of I with benzoylchloride in pyridine gave 73% of III, m.p. 125–126° after two crystallizations from ethanol (lit.[18] m.p. 125.5–126.5°).

2-Phenothiazinyl benzoate (IV). A mixture of 251 g. (0.87 mol.) of III, 50 g. of (1.56 mol.) sulfur and 3.8 g. of iodine was stirred for 1.5 hr. at 160° under dry nitrogen. The extremely hard, green-black reaction mixture was crushed and

(20) R. N. Jones and C. Sandorfy, *Technique of Organic Chemistry*, Vol. 9, *Chemical Applications of Spectroscopy*, A. Weissberger, ed., Interscience Publishers Inc., New York, 1956, pp. 294–296.

(21) A. A. Ebert, Jr., and H. B. Gottlieb, *J. Am. Chem. Soc.*, **74**, 2806 (1952).

(22) A. Roe and W. F. Little, *J. Org. Chem.*, **20**, 1577 (1955), reported a similar removal of a formyl group during the synthesis of various trifluoromethylphenothiazines by Smiles rearrangement of appropriate 2′-formamido-2-nitrodiphenylsulfides.

(23) N. L. Smith, *J. Org. Chem.*, **15**, 1125 (1950).

(24) J. Cymerman-Craig, W. P. Rogers, and M. E. Tate, *Australian J. Chem.*, **9**, 397 (1956).

(25) The known 2-isomers generally melt above 130° and the 4-isomers melt below 120°.

(26) All melting and boiling points are uncorrected.

(27) This compound is mentioned in Swiss Patent No. **283,320** (1952) as having been made from the sodium salt of *m*-hydroxydiphenylamine and acetyl chloride. No data are given. (a) After completion of the work described herein, this compound was reported by J.-P. Bourquin, G. Schwarb, G. Gamboni, R. Fisher, L. Ruesch, S. Guldimann, V. Theus, E. Schenker, and J. Renz. [*Helv. Chim. Acta*, **42**, 259 (1959)].

boiled with 2 l. of benzene. A small amount of black tar was filtered and the benzene solution was decolorized from opaque black to clear maroon by stirring with chromatographic alumina. Concentration and recrystallization from benzene of the resulting cake gave 68 g. (24%) of yellow crystals, m.p. 195.0–196.5°. An analytical sample, obtained by vacuum sublimation followed by crystallization from benzene melted 196–197°.

Anal. Calcd. for $C_{19}H_{13}NO_2S$: C, 71.45; H, 4.10. Found: C, 71.45; H, 4.21.

3-Bromophenyl methyl sulfide (XXI). Diazotization of *m*-bromoaniline, followed by treatment with potassium ethyl xanthate gave *m*-bromothiophenol.[28,29] To a vigorously stirred mixture of 137.5 g. (0.73 mol.) of *m*-bromothiophenol, 380 ml. of 2*N* sodium hydroxide (0.76 mol.) and 670 ml. of water cooled to 10°, was added 105 g. (0.74 mol.) of methyl iodide during 0.5 hr. An additional 50 g. of methyl iodide was then added during 5 min. The reaction mixture was stirred at room temperature for 1.5 hr., extracted with ether and the extracts were dried over anhydrous magnesium sulfate. The yield of XXI was 133 g. (90%), b.p. 83–85/1 mm.; n_D^{23} 1.6243 (lit.[30] b.p. 121°/14 mm.; n_D^{20} 1.6240).

3-Methylmercaptodiphenylamine (V). A mixture of 102 g. (0.5 mol.) XXI, 81 g. (0.6 mol.) of acetanilide, 48 g. (0.35 mol.) of anhydrous potassium carbonate, and 1.7 g. of copper-bronze powder was heated to 220° during 2 hr., and then was stirred and refluxed at an external temperature of 220–230° for 20 additional hr. The final internal temperature was 200°. The black, viscous reaction mixture was extracted with acetone, the acetone was removed under reduced pressure and the dark brown oily residue was refluxed with 500 ml. of 20% ethanolic potassium hydroxide for 4.5 hr. The reaction mixture was poured into a l. of saturated salt solution, extracted with ether, dried over anhydrous magnesium sulfate, and concentrated. Crystallization of the dark brown, viscous residue from petroleum ether (b.p. 35–75°) gave 69 g. (64%) of glistening white crystals, m.p. 54–55°. Another crystallization from the same solvent provided an analytical sample, m.p. 55.0–55.5°.

Anal. Calcd. for $C_{13}H_{13}NS$: C, 72.51; H, 6.09; N, 6.51. Found: C, 72.25; H, 5.98; N, 6.56.

This compound (m.p. 59–61°) was reported by Bourquin *et al.*[6] from the decarboxylation of *N*-(3-methylmercaptophenyl)anthranilic acid.

2-Methylmercaptophenothiazine (VI). A mixture of 96.6 g. (0.45 mol.) V, 26.2 g. (0.82 mol.) of sulfur, and 1.45 g. of iodine was stirred, under nitrogen, for 1 hr. at an internal temperature of 135°. The hard brown reaction cake was dissolved in boiling benzene, treated with Norit and chromatographic alumina and concentrated under reduced pressure. Crystallization of the resulting solid from benzene gave 47 g. (43%) of off-white solid, m.p. 137.5–139.5°. A *pure white* analytical sample was obtained by vacuum sublimation followed by crystallization from ethanol; m.p. 138–139° (lit.[6] *pale yellow* solid, m.p. 138–140°).

Anal. Calcd. for $C_{13}H_{11}NS_2$: C, 63.63; H, 4.52. Found: C, 63.35; H, 4.56.

3-Bromophenyl trichloromethyl sulfide (XXII). Chlorine gas was introduced through a coarse fritted gas dispersing tube into a solution of 284.5 g. (1.4 mol.) of 3-bromophenyl methyl sulfide (XXI) in 1.5 l. of dry chloroform. During chlorine introduction the solution was irradiated with a 150 watt lamp and maintained at +15 to 18°. Chlorine was introduced for 7.5 hr., for a total weight increase of 180 g. Dissolved chlorine was removed with a vigorous nitrogen stream, the solvent was removed under reduced pressure and the residue distilled to give 396 g. (92%) of yellow oil, b.p. 102–104°/1 mm.; n_D^{30} 1.6178.

Anal. Calcd. for $C_7H_4BrCl_3S$: C, 27.43; H, 1.32. Found: C, 27.68; H, 1.54.

3-Bromophenyl trifluoromethyl sulfide (XXIII). A finely ground mixture of 142 g. (0.47 mol.) of XXII and 110 g. (0.62 mol.) of antimony trifluoride was heated in a 250 ml. Claisen flask to 150°. When the initial reaction subsided, the temperature was rapidly raised and the fraction boiling at 190–205° was collected. This fraction was dissolved in ether and washed with 6*N* hydrochloric acid (4 × 150 ml.) and water (2 × 200 ml.). The ether solution was dried over anhydrous magnesium sulfate, the ether was removed, and the residue was distilled to give 73 g. (62%) of colorless liquid, b.p. 192–194°/760 mm.; 103–105°/40 mm.; n_D^{25} 1.5117. This material was used directly in the next step without further purification.

3-Trifluoromethylmercaptodiphenylamine (VII). A mixture of 160 g. (0.62 mol.) of XXIII, 100 g. (0.74 mol.) of acetanilide, 53 g. (0.37 mol.) of anhydrous potassium carbonate, and 2.1 g. of copper-bronze powder was treated as described in the synthesis of V. The residue remaining after removal of the acetone was refluxed for 5 hr. with a mixture of 180 ml. of concentrated hydrochloric acid and 500 ml. of ethanol, poured into 2.5 l. of cold water, and made just alkaline with 20% sodium hydroxide. This mixture was extracted with ether and the extract was dried over anhydrous magnesium sulfate to give 121 g. (72%) of pale yellow oil, b.p. 115–119°/0.3 mm. An analytical sample boiled at 116°/0.3 mm.; n_D^{30} 1.5829.

Anal. Calcd. for $C_{13}H_{10}F_3NS$: C, 57.98; H, 3.74. Found: C, 57.87; H, 3.99.

2-Trifluoromethylmercaptophenothiazine (VIII). A mixture of 117 g. (0.44 mol.) of VII, 25 g. (0.78 mol.) of sulfur, and 1.8 g. of iodine was stirred under nitrogen at 145–160° for 1.5 hr. The reaction mass was dissolved in a liter of boiling benzene, treated with a mixture of Darco G-60 and chromatographic alumina, and concentrated to give a yellow solid. A yield of 58 g. (45%) of glistening yellow crystals, m.p. 165–166°, was obtained on crystallization from carbon tetrachloride.

Anal. Calcd. for $C_{13}H_8F_3NS_2$: C, 52.16; H, 2.69; N, 4.68. Found: C, 51.88; H, 2.69; N, 4.72.

4-Trifluoromethylmercaptophenothiazine (VIIIa). The carbon tetrachloride mother liquor obtained from the crystallization of VIII was concentrated to give a yellow solid. Crystallization from ligroin (b.p. 66–75°) gave 3 g. (2%) of VIIIa, m.p. 82–84°.

Anal. Calcd. for $C_{13}H_8F_3NS_2$: C, 52.16; H, 2.69; N, 4.68. Found: C, 52.34; H, 3.05; N, 4.78.

3-Bromophenyl methyl sulfone (XXIV). A mixture of 22.4 g. (0.2 mol.) of 30% hydrogen peroxide and 20 ml. of glacial acetic acid was added with vigorous stirring, during 35 min., to a mixture of 20 g. (0.1 mol.) of XXI and 140 ml. of glacial acetic acid heated to 40°. When the mildly exothermic reaction had subsided, an additional 10 g. of 30% hydrogen peroxide was added during 5 min. After refluxing for 3 hr. and standing at room temperature overnight the reaction mixture was poured into 400 ml. of cold water. The solid was slurried with cold water, dried and crystallized from carbon tetrachloride to give 20 g. (85%) of glistening white plates, m.p. 99–101°.

This compound was prepared by Twist and Smiles[31] by bromination of methyl phenyl sulfone, m.p. 103°.

3-Methylsulfonyldiphenylamine (IX). This compound was prepared in the same manner as V. Crystallization from carbon tetrachloride followed by recrystallization from benzene–petroleum ether (30–60°) gave 30% of white crystals, m.p. 103–104°. The mixed melting point with XXIV was 70–85°.

(28) H. F. Wilson and D. S. Tarbell, *J. Am. Chem. Soc.*, **72**, 5200 (1950).

(29) D. S. Tarbell and D. K. Fukushima, *Org. Syntheses*, **Coll. Vol. III**, 809 (1955).

(30) Previously prepared by K. Brand, W. Gabel, and E. Rosenkranz (*Ber.*, **70**, 296 (1937)) by means of the Sandmeyer reaction on *m*-aminophenyl methyl sulfide.

(31) R. F. Twist and S. Smiles, *J. Chem. Soc.*, 1248 (1925).

Anal. Calcd. for $C_{13}H_{13}NSO_2$: C, 63.13; H, 5.30; N, 5.66. Found: C, 63.34; H, 5.38; N, 5.57.

Attempted thionation of IX. A mixture of 3.16 g. (0.013 mol.) of IX, 0.74 g. (0.023 mol.) of sulfur and 0.095 g. of iodine was gradually heated in a test tube to 210°. Hydrogen sulfide evolution was extremely slow. Vacuum sublimation of the green, brittle reaction mixture at 180° and 0.05 mm. gave only a trace of yellow solid, m.p. 168–170°. This solid turned green on standing and gave a deep red color with concentrated nitric acid.

2'-Bromo-2-nitro-4-methylsulfonyldiphenylsulfide (XIV). Chlorobenzene was converted to 4-chlorophenyl methyl sulfone using methanesulfonyl chloride and aluminum chloride.[32] Nitration with concentrated sulfuric acid and potassium nitrate gave 3-nitro-4-chlorophenyl methyl sulfone (XI).[31,33] To a mixture of 94.5 g. (0.5 mol.) of *o*-bromothiophenol,[34] 1.5 l. of ethanol, 150 ml. of water and 20 g. (0.5 mol.) of sodium hydroxide was added, with rapid stirring, a suspension of 118 g. (0.5 mol.) of XI in 1 l. of ethanol. The voluminous yellow solid which immediately formed redissolved on heating to reflux temperature. Stirring and refluxing were continued 2 hr. Two identical reactions of this size were filtered hot and combined. From the hot filtrate there separated immediately 135 g. (35%) of long yellow needles, m.p. 131–133°. On cooling, the filtrate yielded an additional 213 g. (55%) of short yellow needles, m.p. 158–160°. On standing overnight, exposed to air at room temperature, the low melting form changed to the high melting form.

Anal. Calcd. for $C_{13}H_{10}BrNO_4S_2$: C, 40.21; H, 2.60. Found: C, 40.54; H, 2.70.

A similar run carried out with 0.05 mol. of XI gave exclusively the long yellow needles, m.p. 132–133° (78%).

Anal. Calcd. for $C_{13}H_{10}BrNO_4S_2$: C, 40.21; H, 2.60; N, 3.61. Found: C, 40.56; H, 2.89; N, 3.64.

2'-Bromo-2-amino-4-methylsulfonyldiphenyl sulfide (XVI). Eleven and six-tenths grams (0.03 mol.) of XIV was added during 0.75 hr., to a mixture of 51.3 g. (0.23 mol.) of stannous chloride dihydrate in 45 ml. of concentrated hydrochloric acid at 50°. The temperature did not rise above 70° during the addition. The clear, pale-yellow reaction mixture was refluxed for 2 hr. and made strongly alkaline with 40% potassium hydroxide. The alkaline mixture was extracted with benzene and the extract was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The resulting pale-yellow oil solidified on standing and gave 7.0 g. (66%) of pure white crystals on crystallization from ethanol, m.p. 125–126°.

Anal. Calcd. for $C_{13}H_{12}BrNO_2S_2$: C, 43.58; H, 3.38; N, 3.91. Found: C, 43.65; H, 3.41; N, 4.21.

2-Methylsulfonylphenothiazine (XIX). A mixture of 78 g. (0.22 mol.) of XVI, 700 ml. of dimethylformamide (DMF), 35 g. (0.25 mol.) of anhydrous potassium carbonate and 3.5 g. of copper-bronze powder was stirred and refluxed for 24 hr. The clear, deep-orange reaction mixture was filtered and the filtrate was diluted with 3 l. of cold water. A green gum formed initially but solidified on standing. The crude solid was dried *in vacuo*, dissolved in benzene, and stirred simultaneously with Norit and chromatographic alumina. Concentration under reduced pressure gave 46.5 g. (77%) of pale yellow solid, m.p. 156.5–158°. An analytical sample melted 158–159° after vacuum sublimation and crystallization from benzene–carbon tetrachloride (lit.[5] m.p. 164°).

Anal. Calcd. for $C_{13}H_{11}NS_2O_2$: C, 56.29; H, 4.00. Found: C, 56.13; H, 3.99.

An attempt to carry out this cyclization in the absence of a solvent and using cuprous iodide instead of copper-bronze was unsuccessful.

4-Bromophenyl methyl sulfide (XXV). 4-Bromobenzenethiol was prepared by reduction of commercial 4-bromobenzenesulfonyl chloride with stannous chloride dihydrate and anhydrous hydrogen chloride in glacial acetic acid.[28,35] Methylation was carried out as described for the synthesis of XXI to give 84% of white solid, m.p. 36.5–38°. A small quantity was further purified by distillation, b.p. 92.5–94°/2.5 mm.; m.p. 39–40°.[36]

This compound was prepared previously by Holt and Reid[36] from 4-aminophenyl methyl sulfide using the Sandmeyer reaction (m.p. reported to be 27°).

4-Bromophenyl trifluoromethyl sulfone (XXVI). Compound XXV was chlorinated and then fluorinated with antimony trifluoride to give 4-bromophenyl trifluoromethylsulfide.[37] Oxidation with 30% hydrogen peroxide in glacial acetic acid, as described in the synthesis of XXIV, gave 93% of white solid, m.p. 59.5–61.5°. This material was dried and used without crystallization. Compound XXVI was previously prepared[37] from 4-aminophenyl trifluoromethylsulfone using the Sandmeyer procedure (lit.[37] m.p. 64–65°).

The oxidation of XXV was also carried out in this laboratory using chromic anhydride in glacial acetic acid. The yields were lower than those obtained with hydrogen peroxide.

4-Chlorophenyl trifluoromethylsulfone (XXVII). Oxidation of 4-chlorophenyl trifluoromethylsulfide,[38] using the same procedure as in the synthesis of XXIV, gave 93% of the sulfone (XXVI), m.p. 55–56° on crystallization from ethanol (lit.[38] m.p. 55–56°).

This oxidation was carried out previously[38] using chromic anhydride in glacial acetic acid.

3-Nitro-4-bromophenyl trifluoromethylsulfone (XII). Seventy-five grams (0.26 mol.) of XXVI were suspended in 240 ml. of concentrated sulfuric acid. The suspension was heated to 80°, at which temperature it became a clear yellow solution. To this solution, maintained at 80–90°, were added, during 55 min., 45.5 g. (0.46 mol.) of solid potassium nitrate. The temperature was maintained at 90° for 2 additional hr. The reaction mixture was poured onto 2 l. of crushed ice and the resulting precipitate was crystallized from ethanol to give 74.8 g. (86%) of white crystals; m.p. 87–89°. An analytical sample was recrystallized from ethanol; m.p. 88–89°.

Anal. Calcd. for $C_7H_3BrF_3NO_4S$: C, 25.16; H, 0.91. Found: C, 25.23; H, 1.04.

3-Nitro-4-chlorophenyl trifluoromethylsulfone (XIII). Nitration of 4-chlorophenyl trifluoromethylsulfone was carried out as described in the synthesis of XII. The yield of fine white needles was 74%; m.p. (from ethanol) 54–55°. A second crystallization from ethanol gave the analytical sample, m.p. 55–56°.

Anal. Calcd. for $C_7H_3ClF_3NO_4S$: C, 29.03; H, 1.04. Found: C, 29.20; H, 1.03.

2'-Bromo-2-nitro-4-trifluoromethylsulfonyldiphenylsulfide (XV). A solution of 71.5 g. (0.21 mol.) of XII in 750 ml. of ethanol was added to a solution of 8.4 g. (0.21 mol.) of sodium hydroxide, 63 ml. of water, 39.9 g. (0.21 mol.) of *o*-bromothiophenol and 625 ml. of ethanol. The resulting yellow solution was refluxed 4 hr. and concentrated to 300 ml. under reduced pressure. The yellow prisms which separated were washed with water in a Waring blendor and then further washed with 300 ml. of ethanol. The yield was 85 g. (92%); m.p. 144–146°.

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Anal. Calcd. for $C_{13}H_7BrF_3NO_4S_2$: C, 35.30; H, 1.60. Found: C, 35.16; H, 1.67.

A similar synthesis of XV using XIII instead of XII gave only a 46% yield after refluxing for as long as 18 hr.

2'-Bromo-2-amino-4-trifluoromethylsulfonyldiphenylsulfide (XVII). A vigorous stream of hydrogen chloride gas was passed into a suspension of 450 g. (2.0 mol.) of stannous chloride dihydrate in 450 ml. of glacial acetic acid and 35 ml. of water until the suspension cleared (*ca.* 10 min.). The temperature of this solution was raised to 65° and 74 g. (0.17 mol.) of XV was added in portions during 1 hr., keeping the temperature at 70–80°. After about two-thirds of the stannous chloride had been added a white solid began to form. On completion of the addition, the reaction mixture was stirred at 85–90° for 2 additional hr. The mixture was filtered and the filtrate was poured onto crushed ice. The resulting precipitate was recrystallized from 95% ethanol to give 58 g. (84%) of white crystals; m.p. 112–113°.

Anal. Calcd. for $C_{13}H_9BrF_3NO_2S_2$: C, 37.87; H, 2.20. Found: C, 38.06; H, 2.40.

2'-Bromo-2-formamido-4-trifluoromethylsulfonyldiphenylsulfide (XVIII). A mixture of 100 g. (0.22 mol.) of XVII and 1 l. of 90% formic acid was refluxed for 20 hr. and poured over 6 l. of crushed ice. The resulting precipitate was washed with water and crystallized from ethanol to give 77 g. (72%) of white needles; m.p. 102.5–103°.

Anal. Calcd. for $C_{14}H_9BrF_3NO_3S_2$: C, 38.19; H, 2.06. Found: C, 38.44; H, 2.17.

2-Trifluoromethylsulfonylphenothiazine (XX) (from XVII). A mixture of 28 g. (0.07 mol.) of XVII, 250 ml. of DMF, 11.6 g. (0.08 mol.) of anhydrous potassium carbonate and 1.4 g. of copper-bronze powder was stirred and refluxed under dry nitrogen, for 6.5 hr. The reaction was then stopped even though carbon dioxide was still being evolved. The reaction mixture was filtered hot, the solid material washed with 25 ml. of DMF and the combined filtrate and washings were poured into 3 l. of water. A yellow colloid formed initially but on standing overnight an orange precipitate separated. The precipitate was dissolved in ethanol, treated with a mixture of chromatographic alumina and Darco G-60, and the solution was diluted with water to give 14 g. (60%) of orange crystals; m.p. 146–147°.

Anal. Calcd. for $C_{13}H_8F_3NO_2S_2$: C, 47.12; H, 2.43. Found: C, 47.27; H, 2.56.

A similar small scale (0.003 mol.) cyclization which was allowed to stir and reflux for 24 hr. gave only 30% of XX.

(*From* XVIII). A mixture of 11 g. (0.025 mol.) of XVIII, 125 ml. of DMF, 4.2 g. (0.03 mol.) of anhydrous potassium carbonate and 0.5 g. of copper-bronze powder was refluxed and stirred, under dry nitrogen, until carbon dioxide evolution was complete (1.25 hr.). The reaction mixture was filtered and washed as in Method A and the combined filtrate and washings were poured into a l. of cold water. On standing at room temperature for 2 hr. the initially formed yellow colloid gave 6.6 g. (80%) of orange crystals, m.p. 145–146° (XX). A mixed melting point with the material obtained from XVII showed no depression.

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PHILADELPHIA, PA.

[CONTRIBUTION FROM THE WYETH INSTITUTE FOR MEDICAL RESEARCH AND THE DEPARTMENT OF CHEMISTRY, TEMPLE UNIVERSITY]

Azacyclooctane Derivatives[1]

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Preparation of 1-methyl-4-phenyl-4-carbethoxyazacyclooctane and α-1,3-dimethyl-4-phenyl-4-propionoxyazacyclooctane is described. These substances showed less analgesic activity than their analogs with six-membered rings.

The preparation of ethoheptazine[3] has made available a seven-membered ring analog of meperidine. This new compound has proved to have valuable analgesic properties without addiction potential.[4] Continuing this study, we have now made the eight-membered ring analog of meperidine to permit study of the effect of further ring enlargement, and particularly because the morphine molecule can be considered to contain an eight-membered heterocyclic ring. In addition to the eight-membered ring analog in this series, namely 1-methyl-4-phenyl-4-carbethoxyazacyclooctane (VI), we have also prepared α-1,3-dimethyl-4-phenyl-4-propionoxyazacyclooctane (XVII), which is an eight-membered ring analog of alphaprodine, a more potent analgesic than either ethoheptazine or meperidine.[5]

Formation of the azacyclooctane ring was ac-

(1) Taken in part from the dissertation of J. Diamond, submitted to the Temple University Graduate Council in partial fulfillment of the requirements for the degree of Doctor of Philosophy (1955).

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(3) The generic name for 1-methyl-4-phenyl-4-carbethoxyazacycloheptane, also known as Zactane®. J. Diamond, W. F. Bruce, and F. T. Tyson, *J. Org. Chem.*, 22, 399 (1957); J. Diamond and W. F. Bruce, U. S. Patent 2,666,050 (1954) [*Chem. Abstr.*, 49, 4031 (1955)]; F. F. Blicke and E.-P. Tsao, *J. Am. Chem. Soc.*, 75, 5587 (1953).

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(5) The synthesis of an azacycloheptane analog of α-prodine will be reported in a subsequent paper.